THE TREATMENT OF ACUTE GLOMERULONEPHRITIS IN CHILDREN*

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Two hundred and nineteen cases of Bright's disease have been diagnosed during the past eight years at the Babies Hospital. This number does not include patients with purulent nephritis or chemical poisoning. These patients with Bright's disease were grouped according to the commonly accepted classification as follows:

Acute Glomerulonephritis	144
Acute → Chronic	2
Chronic Glomerulonephritis	29
Nephrosis	46

There is no good reason to attach much importance to these figures since the great majority of patients with acute nephritis are probably not seen by the doctor. In practice and in the clinic we see the child with a severe infection and a mild nephritis disclosed by routine examination or more rarely the child whose nephritis is severe enough to bring him to the clinic or physician. Our figures simply illustrate the general experience in the eastern cities and show that acute glomerulonephritis and nephrosis are childhood diseases; in adult practice these conditions are relatively uncommon. These figures also show how rarely it is possible to observe the transition from acute to chronic nephritis. I have no explanation for the figures of Snoke and Addis who found that 40 per cent of their patients eventually developed chronic nephritis. I don't think that the difference in technique used in urinalysis accounts for the discrepancy. Perhaps the difference is regional. But chronic nephritis is a complicated controversial problem and my subject tonight is a discussion of some factors in the etiology and treatment of acute glomerulonephritis.

There is abundant evidence that acute glomerulonephritis is preceded and accompanied by hemolytic streptococcus infection with great regularity. The most common seat of infection is in the upper respiratory

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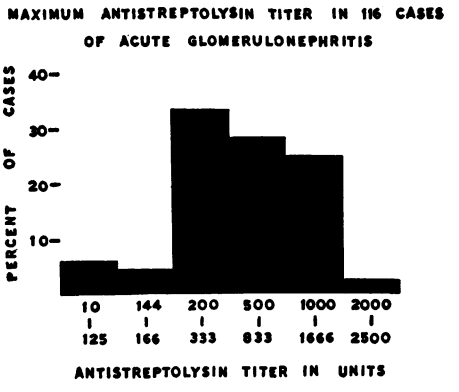

CHART I

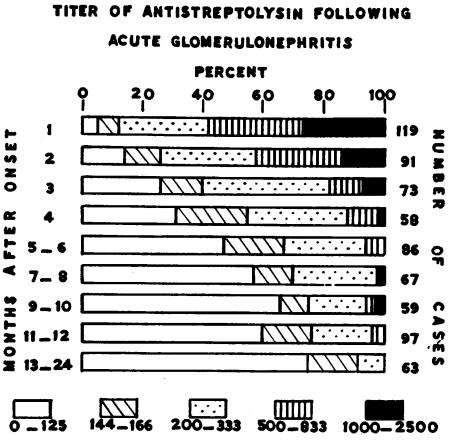

CHART II

tract and adjacent structures. Clinically, we know that the seasonal and geographical incidence of acute nephritis in children parallels that of streptococcus infection. There is no doubt that other organisms can stand in association with typical clinical and anatomical acute nephritis but the number must be small. With Doctor Seegal, Doctor E. N. Loeb and Miss Jost we have studied the antistreptolysin titer of the blood serum in acute nephritis. Chart I shows the maximum antistreptolysin titer of the serum in 116 consecutive cases of acute glomerulonephritis. Ninety-five of these patients are under thirteen years of age, twenty-one are adults. It has been found that in the great majority of normal individuals the antistreptolysin titer is less than 125 units. We think this chart which shows that 9 per cent of patients with acute nephritis have an abnormally high antistreptolysin titer indicates that in New York City the great majority of patients with acute nephritis have had a streptococcus infection preceding the nephritis. In chart II is shown the titer of antistreptolysin in the two years following the onset of acute nephritis. The percentage of normal antistreptolysin titers increases with time until in the second year they are 75 per cent. This period serves as a control for the group. So far as we can tell the variations in antistreptolysin titer are not related in any way to the severity or duration of the acute nephritis but are very closely related to the type and severity and persistence of the streptococcal infection. My object in showing these data is to illustrate the great regularity with which hemolytic streptococcal infection precedes acute nephritis.

The mechanism by which streptococcus infection produces nephritis is not known. It is not by direct bacterial invasion of the kidney. Escherich and Schick suggested as early as 1912 that it "might be a case of hypersensitivity of the organism which is expressed in the ability of small amounts of pathogenic substance to elicit clinical symptoms which at another time would be tolerated without any reaction." They pointed out the analogy between the sequence of events in postscarlatinal nephritis and that in the group of allergic reactions. This is the theory held by most observers today. Masugi and later Farr and Smadel working with nephrotoxic serum have produced a nephritis which clinically and anatomically closely resembles acute and chronic nephritis. However, until the disease is produced by hemolytic streptococcus in the experimental animal many questions must go unanswered.

With this brief discussion on etiology as an introduction I should like to go now to the question of the treatment of children with acute nephritis. Volhard states that in treating acute glomerulonephritis the problem consists in: 1) Preventing the different dangers which may threaten the life of the patient during the acute stage, 2) preventing irreparable organic changes in the kidney. Volhard believes that early diagnosis and proper treatment during the acute stages is an important factor in the prevention of chronic nephritis and goes so far as to say that none of his patients seen and treated in the acute stage develop chronic nephritis. I am unable to convince myself from the evidence available that we can prevent the development of chronic nephritis. However, my experience has led me to believe that early diagnosis and adequate treatment at the proper time may prevent some of the fatalities in the acute stage of the disease.

Table I shows the mortality in acute nephritis in children as reported by different observers.

TABLE I

MORTALITY IN ACUTE NEPHRITIS IN CHILDREN

Cause of Death	*Number*
Infection	28
Cerebral Edema	9
Renal Failure	12
Uremia (type not stated)	13
Cardiac Failure	6
Total Deaths	68 (9.4%)
Total Number of Cases	722

It is seen that forty of sixty-eight deaths were due to cerebral edema, cardiac failure, uremia and renal failure and twenty-eight deaths were due to infection. It is a difficult matter to be certain of the cause of death in acute nephritis. In our own series where death was ascribed to cerebral edema, cardiac or renal failure, infection was an important contributing factor. Clinical experience leads one to believe that in any death from acute nephritis all four conditions may be present in some degree.

The conception that acute glomerulonephritis is but one manifestation of widespread capillary injury is rapidly gaining ground. We have not time to examine the history of this theory or the evidence for its support. The experimental results are conflicting, and much of the evidence is indirect. The physiological mechanisms are not known, but it seems probable that capillary constriction generally, as well as in the glomerular tuft, is an important feature. Baehr contends that unless extrarenal manifestations (edema, hypertension) are present the case is not true acute glomerulonephritis. And he would have us believe that all the glomeruli are involved in the process. From what we do know of etiology and pathogenesis and from anatomical studies in children it seems to me unreasonable to so limit the diagnosis of acute glomerulonephritis. It is known that this disease is an acute often explosive process and that the extrarenal manifestations may occur and not be observed because the patient does not come to the clinic until they have passed. It is also well known that glomeruli do not function continuously and it is reasonable to assume that some of them may escape injury by the hypothetical circulating toxins. This is proven by the work of Oberling who found from a study of biopsy material that the damage was focal and not diffuse. We are concerned here with the fact that clinical manifestations of this generalized capillary involvement are seen in over half of the cases if they are carefully looked for, and in approximately 10 per cent of the cases cerebral and cardiac symptoms and renal shut-down are severe enough to warrant serious therapeutic consideration.

The symptoms and signs which point to cerebral participation in the arteriolar spasm are easily recognized and are present in some degree in over half the children with acute glomerulonephritis. Oliguria, a rising blood pressure, symptoms of increased intracranial pressure, such as nausea and vomiting, headache, somnolence, visual disturbances, slow respiration, and slow pulse are prodromal signs of cerebral edema. There may be an increase in peripheral edema, papilledema and nitrogen reten-

tion may or may not be present, and lumbar puncture may show increased intracranial pressure. When the condition becomes severe, coma, delirium, amaurosis, and convulsions may be added. At autopsy the brain is firm and weighs 20 to 30 per cent more than is normal for the age. The dura is tense, the convolutions are flattened, and the ventricles are compressed. This condition was formerly thought to be uremia, but Volhard showed that it could occur in the presence of normal kidney function and that the term uremia is therefore incorrect.

In the majority of patients urine volume is normal throughout the acute stages. In some patients oliguria develops and may proceed to anuria. This renal shut-down is a serious manifestation. I prefer the term renal shut-down for this condition and use the term true uremia for the condition where the kidney changes are advanced and irreversible. In a few children the nephritis takes a rapidly progressive course and reaches the terminal stage (true uremia) in a short time. But in the majority of children who have impaired renal function associated with anuria during the acute stage complete recovery can and does occur. This condition is best explained on the basis of arteriolar spasm and decreased blood flow through the kidney. As Loeb points out, this idea is supported by the fact that often the anuria is terminated and diuresis appears too suddenly to be explained by the subsidence of inflammatory lesions. Some degree of edema usually goes with this condition, there is failure to concentrate and nitrogen retention and hypertension are present.

In over 60 per cent of the patients with acute glomerulonephritis there is clinical, x-ray, or electrocardiographic evidence of cardiac involvement. The incidence of electrocardiographic changes and x-ray evidence of cardiac enlargement is dependent on the frequency with which such studies are made. In a small number cardiac insufficiency may appear suddenly or develop slowly and result in death. Cardiac dilatation without histological changes is the common finding. Dyspnea or dizziness when the patient sits up, hypertension, a low pulse pressure, or the poor quality of the heart sounds and a systolic murmur may be the only clinical indications of cardiac involvement. The symptoms of cardiac failure are easily recognized.

The anatomical changes, the etiology and pathogenesis of these three conditions are not well understood. The one common factor in all of them is hypertension and the one reliable objective guide to the state of the circulation in acute nephritis is the blood pressure. I think it is impor-

tant for the clinician to realize that when hypertension is present in a child with acute nephritis there are also present these three real threats to life, the danger to the brain, the heart and the kidney.

The successful treatment of cerebral edema was developed in this country by Blackfan. The plan of treatment given here is that advocated by Blackfan and Butler and will serve as a basis for the treatment of cerebral edema, cardiac and renal failure. Any patient with a systolic blood pressure over 115 mm. of Hg., or whose blood pressure is rising, or who has any signs or symptoms of cerebral edema is given 4 to 8 cc. of 25 per cent solution of $MgSO_4$ .7 H_2O intramuscularly. The dose is repeated if the blood pressure has not fallen at the end of two hours or if the blood pressure at a later period begins to rise. With the intramuscular injection 1 to 2 ounces of 50 per cent $MgSO_4$ solution is given by mouth every four hours, until the blood pressure has remained normal for twenty-four hours or until catharsis results. If convulsions are present 1 per cent $MgSO_4$ .7 H_2O, 100 to 150 cc. may be given by vein. This form of therapy is ineffective and contraindicated in all forms of chronic nephritis with hypertension, and the diagnosis should be made before therapy is pushed. Overdosage is indicated by slow, irregular respiration; if this occurs 5 to 10 cc. of 5 per cent $CaCl_2$ should be given intravenously. The physiological action of $MgSO_4$ is not known. Experimental work by Rubin and Rappoport has shown that the inclusion of $MgSO_4$ in the diet of rats inhibits the vascular spasm produced by ergotamine tartrate in rats not so protected. Whatever the explanation empirically we know that $MgSO_4$ lowers the blood pressure, relieves intracranial pressure and increases urine volume.

With this plan of medication fluid intake should be liberal, between 1000 and 1200 cc. per twenty-four hours. The caloric needs may be disregarded until clinical improvement and a return of appetite, when a regular diet may be given. Other measures for the relief of cerebral symptoms, such as lumbar puncture, venesection, and the infusion of 50 per cent sucrose are seldom necessary. Lumbar puncture is not without danger since the sudden withdrawal of large amounts of cerebrospinal fluid in the presence of increased intracranial pressure may induce the medullary cone phase and death.

Oliguria and even complete anuria is at times a difficult problem for the clinician. I have had no experience with diathermy, radiation of the kidneys, renal denervation or decapsulation. The hunger-thirst regime

of Volhard seems to me too drastic for children. In addition to the ordinary measures taken the infusion of saline or hypertonic glucose and $MgSO_4$ intramuscularly or by mouth has seemed to induce diuresis but many times all that is necessary is a little patience.

For those children who have only slight evidence of cardiac involvement nothing more than complete bed rest is indicated. But if cardiac failure develops then in addition to $MgSO_4$ given as outlined above food and fluid should be restricted, venesection is practiced, 50 per cent glucose is given intravenously and digitalis and strophanthus may be used. Chloral hydrate and morphine are good sedatives. I feel that insuring absolute rest will accomplish more for the patient than subjecting him to many procedures of doubtful value.

The other important cause of death in acute nephritis is infection, either *per se* or as a contributory factor present in the circulatory conditions just discussed. Infection and acute nephritis are inseparable but the relationships and mechanisms are unknown. Much has been written on this subject but no one is in a position to speak with authority. For practical purposes the question divides itself into 1) the management of infections during the acute stage and 2) the problem of foci of infection.

In some cases the infection is subsiding by the time the nephritis has appeared, and only conservative therapeutic measures need be considered. But in the majority of patients there is evidence of a complication of the original infection or of a new infection. Peters states it this way: "Nephritis does not usually attack those patients who have an uncomplicated convalescence (from scarlet fever or angina) but those who have a septic complication such as cervical adenitis, otitis media, etc., from which Streptococcus can be recovered". So in some patients infection is a major problem. A mastoiditis, a peritonsillar or retropharyngeal abscess may demand immediate operation. Even if renal function is impaired and hypertension with its threat of cerebral edema and cardiac failure is present, I believe that major surgical indications in these patients should be met at the appropriate time. In these circumstances the nephritis should be regarded as an indication, not a contraindication for operation. Early in the disease we can count on enough renal and cardiac reserve to take the patient through a severe operation. These reserves may not be present if we wait too long. We have never seen harmful effects follow operations performed during the acute stages of the nephritis. Blood transfusion and specific serum therapy may be used whenever they are definitely indi-

cated. There is good clinical evidence that in the majority of cases the proper treatment of severe infection in the acute stages of nephritis has a favorable effect on the course of the disease. We have all seen dramatic improvement in the nephritis follow in a few days after a mastoid operation or the relief of a peritonsillar abscess. But it cannot be said that such measures will prevent the development of chronic nephritis. It is true that some of the children who progress to chronic nephritis have persistent or recurrent infection in spite of proper care early in the disease. But it is also true that many children who have persistent or recurrent infection never develop chronic nephritis. I can only say that adequate surgical treatment of infection in patients with acute glomerulonephritis is fully justified on theoretical and clinical considerations. In my experience this practice has given uniformly favorable results; neglect has been disastrous.

We have used sulfanilamide in a few cases of nephritis with active streptococcus infection. The only thing I can say about it is that if renal function is impaired the level of sulfanilamide in the blood must be carefully watched. Nor can it be stated that the use of this drug early in the course of streptococci infections will prevent the development of acute nephritis.

The problem of foci of infection in children with acute nephritis usually comes down to the questions: 1) Should tonsillectomy be performed? and 2) If so, when is the best time to do it? All agree that the usual indications for tonsillectomy are more easily accepted in a child with nephritis. My own belief is that acute glomerulonephritis is an indication for tonsillectomy. In hospital practice is seems to me a much safer plan to operate on all children. In private practice other circumstances may justify a more conservative policy. But I have not yet learned how to tell what is at the bottom of a tonsil by looking at the outside. Since history, examination, and laboratory tests may be so misleading it would seem much safer to have the tonsils out in any event.

There is a general belief that tonsillectomy should not be done during the acute stages of glomerulonephritis. Some authorities wait for complete recovery or until improvement has stopped. It seems to me that in the ordinary case the time for tonsillectomy is when the hematuria and albuminuria have diminished, when hypertension has subsided, and most important, when the throat is not acutely inflamed. No rule can be made, but in the majority of patients this point is reached in the first two to four months after the onset of acute nephritis. In certain cases there are definite

indications for early tonsillectomy. When during the first few weeks of the disease the nephritis does not improve on a suitable regime, and the otitis or mastoid do not heal as promptly as expected, and when there are repeated attacks of pharyngitis with adenitis with or without exacerbation of the nephritis, tonsillectomy should be considered and performed at the earliest opportunity despite the activity of the nephritis. Parsons and Barling state that "On general principles a focus which is definitely septic (e.g., tonsils) should be removed as soon as possible; but each case must be considered as an independent problem. Operations should not be undertaken during an acute attack of glomerulonephritis without very serious thought; but the general reaction is often surprisingly slight, and the practice is to be commended if the focal inflammation is quite definite and improvement in the kidney trouble is not taking place. There is of course the danger of a very considerable reaction".

The objections to this early attack on foci of infection are in general that it makes the patients worse and specifically that it causes a flare-up in the urine. But if one studies these patients carefully it is seen that the postoperative flare-up is mild and transient and is not accompanied by hypertension or edema, whereas a recurrence of the infection is usually accompanied by a real exacerbation of the nephritis. In my experience I have not seen the evil results predicted by those who have not followed this plan, and therefore this criticism of early tonsillectomy seems invalid.

I admit that we are ignorant of the mechanisms involved, and that no one can say that early tonsillectomy lessens the incidence of infection or prevents chronic nephritis. In considering this problem the following facts seem pertinent: 1) No one can tell which acute cases will progress to chronic nephritis, 2) Acute nephritis is almost invariably preceded and accompanied by upper respiratory infection or one of its complications, 3) Recurrent infection in the convalescent period has an unfavorable effect on the nephritis, 4) The development of chronic nephritis is at times associated with persistent or recurrent infection, 5) When chronic nephritis has become established any attack on foci of infection is useless. These facts lead naturally to the conclusion that anything we can do to fight a condition so closely related to acute and chronic nephritis should be done and done as early as possible. Only long continued observation will bring satisfactory proof; meanwhile one's clinical experience is worth something. In our hands this plan of management has not been harmful and so far the results justify its continuance.

In closing I realize I have omitted to say anything about the general measures taken in the management of acute nephritis. This is not because I think them unimportant but because I think they are well covered in the texts on the subject. I have stressed the problems of infection and circulatory disturbances in acute nephritis in children because they are inadequately treated in most text books and are neglected by many clinicians. My only excuse for spending so much time on the subject is the belief that if the physician will realize these serious possibilities inherent in a child ill with nephritis a more alert attitude will result in a lowered mortality.